

"The Balch (6,983,763) method uses electroosmotic and/or electrophoretic force and turns "ON" electric current through a solution AFTER the solution has come into contact with the substrate. Thus, high polymers are made to move by the effects of the current.

"Our invention is totally different from Balch in that the capillary and substrate are kept at all times apart from each other, thus, no electric current flows. Voltage is applied across the capillary and the substrate so that electric fields are produced. A solution electrified thusly is attracted toward the substrate from the bottom of the capillary. A "marginal" or very small amount of the solution is then made to swell out of the bottom and by the force of attraction, and dribble and be deposited onto the substrate. This method of deposition does not require the substrate to be wetted with the solutions, such as done by Balch. Also, no current need be turned on.

"In the invention , it is possible to deposit an extremely marginal amount of solution at the moment the solution comes into contact with the substrate,since attractive force arises between the solution and the substrate before the contact occurs. Thus, the invention is based on a totally different principle than is applied by Balch, in which the electrophoretic force does not arise until the solution comes into contact with the substrate.

"Please note that although DNA is amplified within the capillary, this has nothing to do with depositing of the solution onto the substrate.

"Also, for the Examiner's edification, PCR can be speeded up by using thinner capillaries. According to our invention, it is

possible to reduce the operating time and prevent contamination with dust, by using both PCR and thin capillaries for spotting DNA solution at the same time.

"The foregoing advantages are nowhere found in the prior art, and surely not in Balch or Haff."

In view of the foregoing, allowance is respectfully solicited.

respectfully

M. KOJIMA

MOONRAY KOJIMA

BOX 627

WWILLIAMSTOWN, MA 01267

Tel (413)458-2880

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WHAT IS CLAIMED IS:

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36. A method of producing biochips comprising the steps of:
arranging a plurality of capillaries having bottom open ends
disposed at predetermined spacing so that said open ends are ad-
jacent to and above a planar substrate, said open ends having dia-
meters which prevent biomolecules from dropping down by force of
gravity under non-depositing condition;

providing said biomolecules in said plurality of capillaries;
providing polymerase chain reaction to amplify said bio-
molecules within said plurality of capillaries;

applying a voltage across said plurality of capillaries and
said substrate during a depositing condition to allow said bio-
molecules to move downward by force of [gravity] ^{attraction} through said open
ends to deposit said biomolecules on sites on said substrate at
space intervals coinciding with said predetermined spacing of said
plurality of capillaries; and

stopping applying of said voltage during said non-depositing
condition so that said biomolecules are held within said plurality
of capillaries by surface tension at said open ends which is greater
than said gravity; whereby

accurate efficient control of said voltage applying causes
uniform and reliable deposits of said biomolecules on said substrate.

37. The method of claim 36, wherein said polymerase chain
reaction is performed by atmospheric temperature change or by
heating with laser irradiation.

APPENDIX "A"

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38. An apparatus for producing biochips comprising:
a plurality of capillaries having bottom open ends arranged
at a same spacing interval as that of sites on a planar substrate
disposed below said open ends of said plurality of capillaries,
said open ends having diameters which prevent biomolecules con-
tained within said plurality of capillaries from falling down by
force of gravity under normal non-depositing state;
amplifying means for providing polymerase chain reaction
to amplify said biomolecules within said plurality of capillaries;
adjusting means for adjusting a gap formed between said open
ends of said plurality of capillaries and said planar substrate
by moving either said plurality of capillaries or said planar
substrate, or both;
transfer means for transferring said biomolecules from said
plurality of capillaries to said sites on said planar substrate
during said depositing state, and for enabling said biomolecules
to remain in said plurality of capillaries during said non-deposi-
ting state, said transfer means comprising:
voltage means for applying voltage across said plurality
of capillaries and said planar substrate so that biomolecules con-
tained in said plurality of capillaries and usually held therein
by surface tension at said open ends are deposited by force of
[gravity] ^{attraction} onto said sites of said planar substrate; and
stopping means for stopping applying voltage so that
said surface tension of said open ends causes said biomolecules

APPENDIX "B"

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to be held within said plurality of capillaries during said non-depositing state against force of gravity;

whereby accurate control of said transfer means produces reliable and uniform biomolecule chips.

39. The apparatus of claim 38, wherein said amplifying means comprises means for providing said polymerase chain reaction by temperature processing.

Add claims 40, 41

Appearing in clear copy

as "New Appendix 'D'"

APPENDIX "C"

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